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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,991	04/13/2006	Lital Alfonta	54-000711US	2082
22798 7590 10/28/2008 QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C. P O BOX 458 ALAMEDA, CA 94501				
EXAMINER				
GEBREYESUS, KAGNEW H				
ART UNIT		PAPER NUMBER		
1656				
MAIL DATE		DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/575,991

Applicant(s)

ALFONTA ET AL.

Examiner

KAGNEW H. GEBREYESUS

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 31, 34, 35, 37-39, 41-44, 46 and 47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 46 is/are allowed.
- 6) ☒ Claim(s) 31, 34, 35, 37-39, 41-44 and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/6/06 & 12/26/06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 145, 2008 has been entered.

Claims 1-30, 32, 33, 36, 40 and 45 are cancelled. Claims 31 and 47 are amended. A discrepancy in the claim listing has come to the attention of the Examiner. Specifically, the status of claims 36 and 37. In the claim amendment of 9/28/07, claim 36 is identified as "currently amended" and claim 37 is cancelled. In the subsequent claim amendment of 4/14/08, claim 36 is identified as cancelled, and claim 37 is identified as "previously presented". The discrepancy has been propagated through the amendments filed 8/14/08.

37 CFR § 1.121(c)(4)(ii) states, "Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim." Thus, claims 36 and 37 are considered cancelled.

Further, 37 CFR § 1.121(c)(4)(i) states, "No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered." Here, claim 37 does not comply with this requirement of 37 CFR § 1.121(c)(4)(i)

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as it recites text. Additionally, the status of claim 37 is improperly identified as 'currently amended' and should be properly identified as 'cancelled' per 37 CFR § 1.121(c).

Furthermore, applicant is reminded that 37 CFR § 1.121(c)(5) states, "A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number." Here, applicant may reintroduce the cancelled claim as a new claim (e.g. claim 48), but may not reuse either claim 36 or 37 which have previously been instructed as cancelled.

Accordingly, in accordance with 37 CFR § 1.121(c), claims 36 and 37 have been treated as cancelled and are not examined.

Claims 31, 34-35, 38, 39, 41-44, 46-47 are present for examination.

All objections and rejections of record that are not maintained are hereby withdrawn.

Claim Objections

Claim 37 is object to because of the following informalities: Claim 37 is objected to for not complying with 37 CFR 1.121(c). On the reply filed on 9/28/08, claim 36 was amended and claim 37 was cancelled. However in the reply filed on 4/14/08 and 8/14/08, claim 37 appears to be re-instated and claim 36 appears to be cancelled. Therefore if Applicants intend to re-instate claim 37, they must add the claim as a "new" claim with a new claim number, according to 37 CFR § 1.121(c)(5) which states, that a claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim

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number." "A claim which was previously canceled may be reinstated."

Appropriate correction is required.

Maintained - Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31, 34-35, 38, 39, 41-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al (US 7, 045,337 B2 / US 2003/0082575 A1 in IDS) in view of Rodriguez et al.

Applicants argue:

"..Claims 45 and 47 are not rejected based on allegations of obviousness. Because the currently amended independent claim 31 incorporates the limitations of claim 45, it cannot be considered obvious...Applicants note that the rejections of record do not allege teachings in the prior art of, e.g., an O-tRNA of SEQ ID NO: 2..."

Applicant's arguments have been carefully considered but not found persuasive. Upon reconsideration of the sequence of the ORS of SEQ ID NO: 2 now encompassed in claim 31 and dependent claims thereof, it appears that this sequence is 100% identical to the ORS of SEQ ID NO: 1 disclosed in Schultz et al. (US 7, 045,337 B2 / US 2003/0082575 A1). Therefore the amendment introducing the specific ORS sequence of SEQ ID NO: 2 do not render the

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instant claims unobvious over the teachings of Schultz et al. See alignment below.

ccggcgguaguucagcagggcgagaacggcgggacucuaaaucgcgucgggucaaaucgggcccgcggaacca SEQ ID NO: 2
ccggcgguaguucagcagggcgagaacggcgggacucuaaaucgcgucgggucaaaucgggcccgcggaacca SEQ ID NO: 1

As previously stated, Applicants claim a composition that comprises a protein with at least two redox active amino acids. To produce the protein composition, Applicants used a screening procedure and identified an ORS/OtRNA pair that can incorporate 3, 4-dihydroxy-L-phenylalanine, a redox active unnatural amino acid, into a protein. Applicants disclose a myoglobin protein comprising a single redox-active amino acid, namely 3, 4-dihydroxy-L-phenylalanine (DHP or L-DOPA) as a working example.

Based on the above teaching which serves as proof of principle for incorporating a redox-amino acid in a protein, Applicants claim a protein comprising at least two redox-active unnatural amino acids selected from 3, 4-dihydroxy-L-phenylalanine, a 3, 4, 5-trihydroxy-L-phenylalanine, a 3-nitro-tyrosine, a 4-nitro-phenylalanine and a 3-thiol-tyrosine in claims 31 and dependent claims 34-35, 38, 39 and 41-44. No sequence limitation for the ORS molecules derived from an *Archaeoglobus fungidis*, a *Methanosarcina mazei*, a *Methanobacterium thermoautotrophicum*, and a *Pyrococcus horikoshii*, is disclosed therefore the rejection of claims 31, 34-35, 38, 39, 41-44 as obvious over Schultz et al in view of Rodriguez et al is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 46 is withdrawn. The amendment incorporated in claim 47 does not overcome the rejection under 35 U.S.C. 112, first paragraph, because this claim now requires an ORS with 90% sequence identity to the ORS of SEQ ID NO: 1 which was not described in the specification.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. "For claims drawn to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses the reduction to practice of ORS of SEQ ID NO: 1 one species within the claimed genus that aminoacylates the corresponding O-tRNA with 3, 4-dihydroxy-L-phenylalanine (DHP) and the

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myoglobin gene with a single selector codon and the myoglobin protein comprising DHP. However this composition is not representative for compositions comprising a genus of synthetases (ORS molecules), with up to 10% sequence variation at any position relative to the synthetase of SEQ ID NO: 1.

The recitation of an ORS with 90% sequence identity represents a partial structure. There is no teaching in the specification regarding which 10% of the structure can vary while retaining aminoacylation activity.

Furthermore the art teaches that variants with activity are identified based on an empirical determination i.e. random variants are produced and screened for ORS molecules with activity.

Although the disclosure of SEQ ID NO: 1 may put one in possession of ORS variants that are 90% identical to SEQ ID NO: 1, the level of skilled and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those ORS molecules that have at least 90% sequence identity to SEQ ID NO: 1 have aminoacylation activity. Thus based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that Applicants were in possession of the claimed genus of ORS molecules in the composition based on the ORS of SEQ ID NO: 1. Therefore claim 47 remains rejected.

Claim 47 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for any ORS variants with 90% identity to SEQ ID NO: 1 where said variants do not necessarily have the function, it does not

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reasonably provide enablement for ORS molecules that are 90% identical to SEQ ID NO: 1 while retaining aminoacylating activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)). The *Wands* factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

One of skill in the art cannot predict *a priori* which polypeptides could be made that are 90% identical and have the requisite function, particularly when the consequences of substitution cannot be determined *a priori*. The specification does not provide an example of any ORS sequence with up to 10% variation (up to 30 amino acids) relative to SEQ ID NO: 1. Furthermore no guidance regarding the residues that bear upon the structure that in turn affect aminoacylation activity are provided. With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable. For example, RUDINGER (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (Page 6).

Without sufficient guidance, determination of ORS molecules with up to 30 amino acid variation in a 306 amino acid protein having aminoacylating activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Conclusion:

Claim 46 is allowable if re-written in an independent form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose

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telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus PhD/
Examiner, Art Unit 1656

/Andrew D Kosar/
Primary Examiner, Art Unit 1654